

REMARKS

Upon entry of the present amendment, claims 1-13, 20, and 22 will be pending in the present application. Claim 22 remains pending but withdrawn; claim 21 is canceled by the present amendment; and claims 14-19 and 23 were canceled previously.

Claim 1 has been amended to specify that the patient is a human patient. This amendment is supported by original claim 21 (which is now canceled). The preamble of claim 1 has also been amended to emphasize the *predictive* value of the methods claimed. The specification describes "a method for the *prediction* and diagnosis of heart dysfunction" (*see, e.g.*, the specification at page 4, lines 26-27, and original claim 13). No new matter has been added.

Information Disclosure Statement (IDS)

Applicant respectfully note that the references cited on the IDS filed on February 18, 2004 have not been initialed or considered by the Examiner. Applicant requests that the Examiner consider these references and return an initialed copy of the IDS to applicants.

35 USC § 103(a)

Applicants note with appreciation the withdrawal of all prior rejections, including the prior rejections for obviousness. The claims are now rejected, however, on the basis of new obviousness rejections; the Examiner has recombined various references against various claims. In view of the amendment of claim 1 and the remarks that follow, the Examiner is asked to reconsider and withdraw the present grounds for rejection.

1. Claims 1-3, 6-13, and 20-21 were rejected as obvious over Puyo *et al.* (*Regulatory Peptides* 105:139-143; "Puyo") and Motwani *et al.* (*Lancet* 341:1110-1113; "Motwani").

The Examiner characterizes Puyo as describing "a method of determining atrial natriuretic peptide (ANF) levels in patients that are myocardial compromised (the Title and page 139)" (Office action at page 4). Regarding the factors recited in the present claims, ANF

and BNP, the Examiner further notes that Puyo teaches "that myocardial failure leads to increased ventricular production of ANF and BNP" (Office action at pages 4-5). While Puyo, in introducing her study, does state that "[t]he cardiac hypertrophy that accompanies myocardial failure leads to increased ventricular production of ANF and BNP" (Puyo at page 139), Puyo did not suggest BNP could be used in predicting cardiomyopathies or myocarditis and did not analyze BNP at all. The Examiner recognizes this, stating, "Puyo et al do not teach determining BNP levels in patients that are myocardial compromised" (Office action at page 5). Thus, Puyo's study cannot suggest analysis of BNP, as required by the present claims.

Further, Puyo *teaches away* from the subject matter presently claimed. Puyo found that ANF could not be used to determine which patients will develop myocardial disease. More specifically, Puyo states (at pages 141-142):

Our study shows that plasma ANF levels are elevated in patients with CD [conduction defects] and CHF [chronic heart failure] of different origins, but the peptide neither permits to differentiate chagasic from non-chagasic cardiac alterations, except in CHF patients, nor to detect early which patients will develop myocardial disease from those which will not, after 1 year of follow-up.

And (pages 142-143; emphasis added):

In conclusion, in the present work, we determined for the first time ANF levels in different stages of Chagas' disease, and found that: (1) ANF levels alone were not able to differentiate chagasic cardiomyopathy from others of different etiology; (2) *plasma ANF does not seem to be a prognostic marker of future development of chagasic heart disease in asymptomatic patients when they were studied during a short time period (1 year)*; perhaps a longer period of follow-up of that group of patients could be necessary to evaluate its prognostic value; (3) ANF is a sensitive marker capable of detecting gradual impairments in cardiac function in all patients studied.

Thus, Puyo not only fails to describe methods that include analysis of BNP levels, but also concludes that ANF is not effective in predicting the development of chagasic heart disease. The speculation that prognostic value might be found if the analysis were extended beyond one year is just that -- speculation.

The Examiner has combined Puyo with the teachings of Motwani. The Examiner characterizes Motwani as teaching that "in chronic heart failure, plasma BNP concentrations are

substantially increased, [and] the circulating concentration is proportional to the severity of heart failure (page 1111)” (Office action at page 5). The Examiner then concludes that it would have been *prima facie* obvious to modify Puyo’s method, which consisted of assessing ANF levels, to include the determination of BNP levels “because Puyo et al teach that myocardial failure leads to increased ventricular production of ANF and BNP” (Office action at page 6).

Applicant disagrees, particularly in view of the present amendment of claim 1. Motwani is entirely focused on patients who have already suffered a myocardial infarction (a heart attack), with the results indicating that “measurement of circulating BNP may afford a simple means of identifying those patients likely to benefit from ACE inhibition postinfarction...” (Motwani at page 112, right-hand column). There is no suggestion at all that one should assess BNP in order to predict whether cardiomyopathy or myocarditis will arise as a result of an infection.

Unlike Motwani or Puyo, Applicant has shown that elevated levels of BNP (or BNP and ANF) in a patient suffering from an infection correlate with a diagnosis of cardiomyopathy and/or myocarditis even before the disease has progressed far enough for the patient to exhibit clinical signs of cardiomyopathy or myocarditis. The method now claimed can be used to diagnose infection-related cardiomyopathy or myocarditis early on, which is clearly beneficial because it allows for therapeutic intervention and monitoring early in the disease process. This advance in the field of infectious disease medicine was not suggested by Puyo or Motwani, either alone or in combination. Puyo not only failed to analyze BNP levels, but also failed to establish any link between ANF levels and the likelihood that heart disease would arise following an infection in the patient. This significant shortcoming cannot be remedied by Motwani because Motwani examined an entirely different patient population; Motwani assessed patients after they had suffered a heart attack. The fact that “myocardial failure *leads to* increased ventricular production of ANF and BNP” (Office action at page 6; emphasis added) is simply not sufficient. There is no reason to think that what happens *after* a patient has a heart attack (or experiences heart failure) would be predictive. There is nothing in the prior art to suggest that BNP (or BNP and ANF) should be assessed *before* cardiomyopathy or myocarditis is evident, let alone in a patient who has an infection.

The facts here are very different from the facts in *KSR International Co. v. Teleflex Inc.*, 127 S.Ct. 1727 (2007). In *KSR*, the invention was a rather straightforward mechanical device – a

modified gas pedal. Here, Applicant has not simply combined two familiar elements according to known methods to yield a predictable result. Although ANF and BNP have been assessed in the art, there is nothing in the art to suggest that BNP alone or BNP and ANF together would reliably indicate whether cardiomyopathy or myocarditis will arise as a result of an infection.

In view of the foregoing, Applicant respectfully requests that this rejection be withdrawn.

2. Claims 1-3, 6-13, and 20-21 were rejected as obvious over Scaglione *et al.* (*J. Parasitol.* 87:923-6; "Scaglione") and Motwani. Applicant respectfully disagrees.

The Examiner contends that Scaglione teach a method of determining ANF levels in subjects having myocarditis produced by *T. cruzi* infection, *i.e.*, Chagas disease. The Examiner also contends that Scaglione teaches that ANF and BNP are continuously released from the heart and they are found to be elevated in different types of cardiovascular diseases.

Applicant acknowledges that methods of determining ANF levels are known, and that ANF and BNP have been found to be elevated in different types of cardiovascular diseases. This background information is recited in the introductory paragraphs of Scaglione as is noted by the Examiner. However, it was not known, nor would it have been obvious to one skilled in the art at the time of the invention, that elevated BNP levels in a patient can be used to diagnose or predict potential for developing cardiomyopathy or myocarditis caused by infection.

Further, Scaglione does not disclose or suggest a method of determining BNP. Rather, Scaglione reports the results of testing ANF levels in *T. cruzi*-infected Sprague-Dawley rats. While these levels are found to be elevated in the infected rats during the acute and chronic phases, this is reported to be inconsistent with prior findings, *see* Scaglione page 925, first column, lines 27-34 as follows:

Following the acute phase of *T. cruzi* infection, Piazza *et al.* (1994) found that the increased plasma ANF levels return to normal values. In this work, an increase of plasma ANF levels was also found during the acute phase. However, in the present study, the concentration of the peptide was found to be elevated in the chronic phase of the disease. These apparently inconsistent results could be due to the differences in the rat-*T. cruzi* model system used in the 2 studies.

The findings of Scaglione are not based on direct clinical testing in human patients, but are based on an analysis in one example of a rat model of the disease. The inconsistency noted by Scaglione, *i.e.* whether increased plasma ANF persists into the chronic phase of infection, is particularly important for a method of diagnosing or predicting a patient's potential to develop chagasic cardiomyopathy or myocarditis, or other forms of cardiomyopathy or myocarditis caused by infection. This is apparent from Scaglione's silence on whether ANF would be a useful marker in such a method. Further, as noted in Applicant's last reply to the Office action of March 25, 2008, Scaglione is authored by four of the investigators of Puyo (*supra*), and was published one year earlier than Puyo. Puyo thus can be interpreted to represent an attempt by the Scaglione authors to verify their earlier findings in Sprague-Dawley rats using human subjects. As discussed above, Puyo concludes that ANF is not an effective marker for prognosis of future development of chagasic heart disease. Thus, the deficiencies of Puyo are shared by Scaglione.

As discussed above, Applicant has shown that elevated BNP levels in a patient can be used to diagnose or predict a patient's potential for developing chagasic cardiomyopathy or myocarditis, or other forms of cardiomyopathy or myocarditis caused by infection. This result cannot be obtained or surmised from Scaglione's study of ANF, particularly in view of the acknowledged inconsistency in their rat data from earlier findings, and since essentially the same authors conclude in Puyo that ANF alone is not a useful prognostic marker.

The Examiner has attempted to overcome the deficiencies of Scaglione by combining this reference with the teachings of Motwani. Specifically, the Examiner acknowledges that Scaglione does not teach determining BNP levels in patients that are myocardial compromised, but contends that methods of determining BNP levels are known from Motwani.

As discussed above, Motwani does not disclose or suggest a method of determining BNP levels to assist in the diagnosis of cardiomyopathy or myocarditis that arises as a result of an infection as defined in the claims of the instant application. Rather, Motwani studies a series of patients after myocardial infarction.

Applicant has shown, unlike Motwani or Scaglione, that elevated levels of BNP are detected after a patient suffers an infection, *e.g.*, Chagas disease, and these levels correlate with a diagnosis of infection-related cardiomyopathy and/or myocarditis even before the disease has progressed far enough to exhibit clinical signs of cardiomyopathy or myocarditis. This result

cannot be obtained through a combination of the Scaglione and Motwani references, particularly since one skilled in the art would also be expected to seek out the later publication of Puyo.

The shortcomings of Scaglione (with or without reference to Puyo), which are not only that they fail to analyse BNP levels as the Examiner suggests but that they also fail to connect ANF levels to a useful prognostic marker of infection-related cardiomyopathy or myocarditis, are not remedied by Motwani. Motwani does not study BNP levels in infection-related cardiomyopathy and/or myocarditis and therefore, one skilled in the art would not be able to deduce that BNP levels are useful in diagnosing infection-related cardiomyopathy and/or myocarditis without undue experimentation.

Accordingly, Applicant submits that claims 1-3, 6-13, and 20-21 are not rendered obvious by Scaglione and Motwani, and respectfully request that this ground for rejection be reconsidered and withdrawn.

3. The Examiner rejected claim 4 under 35 USC § 103(a) as unpatentable over Scaglione and Motwani as applied to claims 1-3, 6-13, and 20-21, and further in view of Marumo *et al.* (*Clinical Chem.* 36:1650-1653; "Marumo (1990)"). Applicant disagrees and traverses the rejection based on the following.

In making this rejection, the Examiner refers to the teachings of Scaglione and Motwani as they apply to Applicant's claims 1-3, 6-13, and 20-21. As discussed above, the combined teachings of Scaglione and Motwani do not render the claimed methods obvious. Marumo (1990) is combined with Scaglione and Motwani by the Examiner to establish the limitation of claim 4, *i.e.*, that the body fluid used in the testing procedure is urine. While Marumo (1990) does establish that atrial natriuretic peptide (ANP) is present in urine, it does not address the other shortcomings of Scaglione and Motwani. In particular, Marumo (1990) does not show that increased BNP levels is a useful marker of infection-related cardiomyopathy or myocarditis, and therefore, one skilled in the art would not be able to come to the subject matter of claim 4 without undue experimentation.

Accordingly, Applicant submits that claim 4 is not rendered obvious by Scaglione, Motwani, and Marumo (1990), and respectfully request that this rejection under 35 U.S.C. § 103(a) be reconsidered and withdrawn.

4. Claim 5 was rejected under 35 USC § 103(a) as unpatentable over Scaglione and Motwani as applied to claims 1-3, 6-13, and 20-21, and further in view of Marumo *et al.* (*Journal of Endocrinology* 119:127-131; "Marumo (1988)"). Applicant disagrees and traverses the rejection for the following reasons.

In making this rejection, the Examiner refers to the teachings of Scaglione and Motwani as they apply to claims 1-3, 6-13, and 20-21. As discussed, the combined teachings of Scaglione and Motwani do not render the stated claims obvious. Marumo (1988) is combined with Scaglione and Motwani by the Examiner to establish the limitation of claim 5, *i.e.*, that the body fluid used in the testing procedure is cerebrospinal fluid. While Marumo (1988) does establish that atrial natriuretic peptide (ANP) is present in canine cerebrospinal fluid, it does not address the other shortcomings of Scaglione and Motwani. In particular, Marumo (1988) does not show that increased BNP levels is a useful marker of infection-related cardiomyopathy or myocarditis, and therefore, one skilled in the art would not be able to come to the subject matter of claim 5 without undue experimental burden.

Applicant accordingly submits that claim 5 is not rendered obvious by Scaglione, Motwani, and Marumo (1988), and respectfully request that this ground for rejection be reconsidered and withdrawn.

CONCLUDING FORMALITIES

In light of the claim amendments discussed and made herein, Applicant submits that the pending claims are allowable and request early and favorable action thereon.

Early allowance of this application based on its merits is respectfully requested.

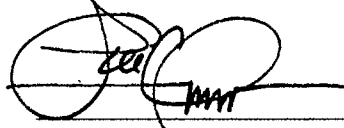
The fee in the amount of \$490 for the Petition for Extension of Time fee is being paid on the electronic filing system by way of deposit account authorization. Apply any other charges or credits to deposit account 06-1050, referencing attorney docket 14703-0002001.

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Respectfully submitted,

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A handwritten signature in black ink, appearing to read 'Lee Crews', written over a horizontal line.

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